CASE: **MA0095 NP**

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Burton Rodney
Type or print name

Signature

December 12, 2005
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
MANOJ NERURKAR ET AL.
APPLICATION NO: **10/642,366**
FILED: **08/14/2003**
FOR: **ARIPIPRAZOLE COMPLEX FORMULATION AND METHOD**

ART UNIT: **1623**
EXAMINER: **MAIER, LEIGH C**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF PRIOR INVENTION OF MANOJ NERURKAR AND VIJAY NARINGREKAR TO OVERCOME CITED U.S. PATENT PUBLISHED APPLICATION U.S. 2002/0193438 A1 (37 C.F.R. §1.131)

To the Commissioner for Patents and Trademarks:

1. This Declaration is to establish reduction to practice of the invention in this application at a date prior to April 25, 2001, that is the priority date claimed in U.S. 2002/0193438 A1.

2. Manoj Nerurkar and Vijay Naringrekar declare as follows.

3. That they are employed by Bristol-Myers Squibb Company, the assignee of the subject application as evidenced by an assignment signed by each and recorded at the U.S. Patent and Trademark Office on September 17, 2003, Reel 103985, Frame 0962 (ATTACHMENT I).

4. That they are the inventors, together with Mark Dominick, of the invention claimed in U.S. patent application Serial No. 10/642,366 filed August 14, 2003.

5. That the invention defined in the claims as filed was conceived and reduced to practice in the United States prior to April 25, 2001.

6. That prior to April 25, 2001 Manoj Nerurkar and Vijay Naringrekar conceived of the concept of solubilizing aripiprazole by complexing it with a β-cyclodextrin and Mark Dominick together with Manoj Nerurkar and Vijay Naringrekar conceived of an injectable aripiprazole formulation which produces minimal irritation at the injection site.

7. That prior to April 25, 2001, Manoj Nerurkar carried out experiments to increased solubility of aripiprazole by forming complexes of aripiprazole with various β-cyclodextrins, such experiments being recorded in Bristol-Myers Squibb Notebook No. 42671 cover page (ATTACHMENT A) and pages 122, 132, 133, 134, 135 and 136, copies of which pages are attached hereto and identified as ATTACHMENTS B, C, D, E, F and G, respectively.

8. On Notebook page 122 (ATTACHMENT B), entitled "Project No. 030D8, Experiment No. 44, Solubility Screening Studies with BMS-337039 (Aripiprazole)", Manoj Nerurkar recorded experiments which he carried out prior to April 25, 2001, wherein he prepared a mixture of aripiprazole in 10% hydroxypropyl β-cyclodextrin in water (HPBCD) and in 10% sulfobutyl ether β-cyclodextrin (SBECD) in water, whereby it is seen that solubility of aripiprazole was improved from 0.0001 mg/mL in water to 0.02 mg/mL in HPBCD and 0.12 mg/mL in SBECD.

Page 122 was signed by Manoj Nerurkar and witnessed by Sunita Borsadia prior to April 25, 2001, the effective date as a reference of U.S. 2002/0193438 A1.

9. On Notebook pages 132, 133 and 134 (ATTACHMENTS C, D and E, respectively), entitled "Project No. 030D81, Experiment No. 49, Combination of pH adjustment and SBECD complexation", Manoj Nerurkar recorded experiments which he carried out prior to April 25, 2001,

wherein the objective was "to determine if SBECD forms a complex with aripiprazole either in ionized or salt form of a drug". Pages 132, 133 and 134 describe preparation of solutions of complexes of aripiprazole and SBECD (Captisol®) in HCl (Batch A) or in lactic acid (Batch B) having a pH ranging from 4.12 to 5.2 (Batch A in HCl).

Notebook pages 132, 133 and 134 were signed by Manoj Nerurkar and witnessed by Sunita Borsadia prior to April 25, 2001, the effective date as a reference of U.S. 2002/1093438 A1.

10. On Notebook pages 135 and 136 (ATTACHMENTS F and G, respectively), entitled "Project 030D8, Experiment No. 50, Effect of Increasing Conc. of Cyclodextrins (SBECD) on Equilibrium Solubilities of BMS-337039-01 [Aripiprazole] at Various pHs" Manoj Nerurkar recorded experiments which he carried out prior to April 25, 2001. As seen on pages 135 and 136, solutions of aripiprazole in 5, 10, 15 and 20% SBECD and a solution of aripiprazole in 20% HPBCD were prepared, each of whose pH was adjusted with HCl. As seen in the second table on page 136, solubility of the aripiprazole in the SBECD and HPBCD increased markedly with decreasing pH.

As seen on page 122, solubility of aripiprazole in water is 0.0001 mg/mL. As seen on page 136, solubility of aripiprazole in 5% SBECD at pH ranging from 6.4 to 4.8 has a solubility ranging from 0.65 to 7.29 mg/mL; aripiprazole in 10% SBECD at pH ranging from 6.4 to 4.8 has a solubility ranging from 1.31 to 14.51 mg/mL; aripiprazole in 15% SBECD at pH ranging from 6.4 to 4.8 has a solubility ranging from 2.11 to 18.19 mg/mL and aripiprazole in 20% SBECD at pH ranging from 6.4 to 4.8 has a solubility ranging from 2.7 to 24.96 mg/mL.

It is therefore concluded that the increase in solubility of the aripiprazole is due to its complexation with the β-cyclodextrin which clearly establishes reduction to practice of the invention as claimed.

11. Manoj Nerurkar signed each of the pages 135 and 136 but inadvertently failed to date his signature. However, Sunita Borsadia witnessed both pages by signing and dating both pages prior to April 25, 2001. Accordingly, it can only be concluded that Manoj Nerurkar signed the notebook pages 135 and 136 prior to April 25, 2001.

12. The actual dates of Experiments 44, 49 and 50 were carried out and the dates of signing by Manoj Nerurkar and witnessing by Sunita Borsadia, were all prior to April 25, 2001, but have been obliterated.

13. The above clearly establishes conception and reduction to practice of the invention covered by the relevant claims of the subject patent application (vis-à-vis U.S. published patent application 2002/0193438) prior to April 25, 2001.

14. This Declaration is submitted prior to Final Rejection.

15. The undersigned declares further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of application Serial No. 10/642,366 or any patent issued thereon.

Date: Dec. 7, 2005

MANOJ NERURKAR

Date: Dec. 7, 2005

VIJAY NARINGREKAR

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SEPTEMBER 22, 2005

PTAS

700044478A

BRISTOL-MYERS SQUIBB COMPANY
STEPHEN B. DAVIS
P.O. BOX 4000
PRINCETON, NJ 08543-4000

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 09/17/2003

REEL/FRAME: 013985/0962
NUMBER OF PAGES: 6

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
NERURKAR, MANOJ

DOC DATE: 09/03/2003

ASSIGNOR:
NARINGREKAR, VIJAY

DOC DATE: 09/03/2003

ASSIGNOR:
DOMINICK, MARK

DOC DATE: 09/15/2003

ASSIGNEE:
BRISTOL-MYERS SQUIBB COMPANY
LAWRENCEVILLE-PRINCETON ROAD
PRINCETON, NEW JERSEY 08543-4000

SERIAL NUMBER: 10642366
PATENT NUMBER:

FILING DATE: 08/14/03
ISSUE DATE:

ATTACHMENT I

TONYA LEE, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

OIPE 09/17/2003
RECORDATION FORM COVER SHEET 700044478
PATENTS ONLY
DEC 14 2005

FORM PTO-1595
(Rev. 6-93)
OMB No. 0651-0011 (exp. 4/94)

DEPARTMENT OF COMMERCE
Patent and Trademark Office

To the Honorable Director of the US Patent and Trademark Office: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):
Manoj Nerurkar, Vijay Naringrekar, Mark Dominick

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies)
Name: Bristol-Myers Squibb Company
Internal Address:
Street Address: Lawrenceville-Princeton Road
City: Princeton State: NJ ZIP: 08543-4000
Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other
Execution Date: September 3, 2003, September 15, 2003

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is:
A. Patent Application No.(s)
10/642,366
B. Patent No.(s)
Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:
Name: Stephen B. Davis
Internal Address: Bristol-Myers Squibb Company
Patent Department
Street Address: P.O. Box 4000
City: Princeton State: NJ ZIP: 08543-4000

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41) $ 40
☐ Enclosed
☒ Authorized to be charged to deposit account and any other additional fees required.

8. Deposit account number:
19-3880 (in the name of Bristol-Myers Squibb Company)
(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Burton Rodney
Name of Person Signing
Reg. No. 22,076

Signature

September 17, 2003
Date

☐ Certificate of mailing on reverse side

Total number of pages including cover sheet, attachments, and document: 6

Mail documents to be recorded with required cover sheet information to:
Mail Stop Assignment Recordation Services, Director of the US Patent and Trademark Office
PO Box 1450, Alexandria, VA 22313-1450

ASSIGNMENT

We,

Manoj Nerurkar	residing at	83 Regal Drive Monmouth Junction, New Jersey 08852 United States of America
Vijay Naringrekar	residing at	538 Burlington Street Paramus, New Jersey 07652 United States of America
Mark Dominick	residing at	10540 Wilmington Drive Evansville, Indiana 47725 United States of America,

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Lawrenceville-Princeton Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

ARIPIPRAZOLE COMPLEX FORMULATION AND METHOD

invented by us and described in the non-provisional United States patent application

Application No. 10/642,366, filed August 14, 2003,

including said non-provisional United States patent application and any application claiming priority from said non-provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries.

Worldwide
Case MA 0095 NP

Signed this 3rd day of September, 2003 by Manoj Nerurkar
Manoj Nerurkar

STATE OF New Jersey)
) **ss.**
COUNTY OF Middlesex)

On the 3rd day of September, 2003, before me came Manoj Nerurkar, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

Laura H. Derbin
Notary Public

LAURA H. DERBIN
NOTARY PUBLIC, STATE OF NEW JERSEY
ID # 2278973
Commission Expires Sept. 7, 2006

Signed this 3rd day of September, 2003 by

Vijay Naringrekar

STATE OF New Jersey)
) **ss.**
COUNTY OF Middlesex)

On the 3rd day of September, 2003, before me came Vijay Naringrekar, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

Laura H. Derbin
Notary Public

LAURA H. DERBIN
NOTARY PUBLIC, STATE OF NEW JERSEY
ID # 2278973
Commission Expires Sept. 7, 2006

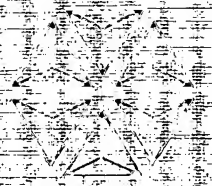
Signed this 15th day of September, 2003 by Mark Dominick
Mark Dominick

STATE OF)
) **ss.**
COUNTY OF)

On the 15th day of September, 2003, before me came Mark Dominick, to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

Linda Jo Henzman
Linda Jo Henzman
Notary Public

[SEAL]



BRISTOL-MYERS SQUIBB

PHARMACEUTICAL RESEARCH INSTITUTE

DATE: _____ PROJ. NO. 03008 EXPT. NO. 44

SUBJEC: Timed

Solubility Screening Studies with BMS-337039 (Aripiprazole)

	Solvent	Solubility, mg/mL	Data File
	Water	0.0001	Nerurkam\aripi\4198
	Ethanol	3.2	Nerurkam\aripi\4198026
	Propylene Glycol	0.97	Nerurkam\aripi\4198018
	Polyethylene Glycol 300 (PEG 300)	14.0	Nerurkam\aripi\4198019
	Polyethylene Glycol 400 (PEG 400)	12.7	Nerurkam\aripi\4198020
	10% Polyethylene Glycol 3350 (PEG 3350) in water	0.002	Nerurkam\aripi\4198021
1	Triacetin	3.5	Nerurkam\aripi\4198022
	1% Egg Lecithin +1% Bile Salts (So. Cholate+deoxycholate) in water	0.05	Nerurkam\aripi\4198023
	10% PVP in water	0.3	Nerurkam\aripi\4198024
	N,N-Dimethyl Acetamide (DMA)	171.5	Nerurkam\aripi\4198025
	10% Hydroxy propyl beta cyclodextrin in water	0.02	Nerurkam\aripi\4198027
	10% Sulfabutyl ether beta cyclodextrin in water	0.12	Nerurkam\aripi\4198028
	Oleic Acid	>300	-
1	Ethyl Oleate	1.13	Borsadis\aripi\4239005
	Peanut Oil	0.86	Borsadis\aripi\4239001
	Soybean Oil	0.86	Borsadis\aripi\4239002
	Cottonseed Oil	1.19	Borsadis\aripi\4239003
	Sesame Oil	0.82	Borsadis\aripi\4239004
	Hexanoic Acid	> 200*	-
	Octanoic Acid	> 200*	-
2	Captex (medium chain triglyceride, C8 + C10)	2.46	Borsadis\aripi\4239010
	PEG 400:EtOH (50:50)	12.43	Nerurkam\aripi\4198013
	PEG 400:EtOH: 1% Tween 80 in water (30:30:40)	0.35	Nerurkam\aripi\4198057
	PEG 400:EtOH: 1% Solutol in water (30:30:40)	0.33	Nerurkam\aripi\4198058
	Oleic Acid: Soybean Oil (10:90)	9.55 (?)	Borsadis\aripi\4239006
	Oleic Acid: Soybean Oil (25:75)	29.57 (?)	Borsadis\aripi\4239007
2	Oleic Acid: PEG 400 (10:90)	20.23 (?)	Nerurkam\aripi\4198018
	1 % Decanoic Acid in Soybean Oil	2.77	Borsadis\aripi\4239008
	5 % Decanoic Acid in Soybean Oil	2.69	Borsadis\aripi\4239009

30 The table will be updated periodically with more studies and also when a better assay for oily systems is developed.

35

ATTACHMENT B

M. Nerurkar

WITNESSED AND UNDERSTOOD BY:

REFERENCES:

DATE _____ PROJ. NO. 03008 EXPT. NO. 49

SUBJECT Combination of pH adjustment & SBECD complexat

Objective of this experiment is to determine if SBECD forms a complex with Aripiprazole either in ionized or salt form of a drug.

From previous experience, we know that when the pH is adjusted with HCl, the drug gets ionized. It's solubility goes upto 0.8 mg/ml at pH 3.0. However it did not form a HCl salt (DSC on excess solid)

On the other hand, when the pH is adjusted with Lactic Acid, the solubility goes upto 8 mg/ml and the solid phase is different on DSC than the drug itself (Expt #45 pg 124). Determining solubility of drug in presence of SBECD using pH adjustment approaches either with Lactic Acid or HCl will tell us if the drug forms complex, whether it is with ionized form or with lactate salt.

Batch A: pH adjustment with HCl

To about 20 ml water, add 5 g SBECD (20% SBECD in final volume of 25 ml) To this add drug (200mg) Adjust pH with 1N HCl. Drug starts dissolving. At pH 4.0 the solution is clear.

Add 200 mg more drug - pH starts rising up. Adjust with 1N HCl. Drug completely dissolved. pH = 4.1

Add 200 mg more and adjust pH to 4.0. q.s. to 25 ml

So far 600 mg drug in 25 ml i.e about 24 mg/ml

This solution can be supersaturated or drug may be more soluble in this medium. Filter this solution. Divide in 2 parts in 10 ml vials

Store 1 vial at RT, one at 8°C and one at -70°C

ATTACHMENT C

SIGNED M. Nesnas/Cas DAT

WITNESSED AND UNDERSTOOD BY: Gentes DATE

DATE: PROJ. NO. 03008 EXPT. NO. 49.

SUBJECT Continued

Batch B: pH adjustment with Lactic Acid.

Perform experiment similar to this except for adjusting pH with Lactic Acid.

200 mg drug: pH 3.5 clear
+ 200 mg drug " "
+ 200 mg drug " "

Filter the solutions, divide and store as reported under Batch A.

To excess solutions from batch A and B, add excess drug. Equilibrate at RT. The ~~se~~ saturation solubilities & whatever pH ~~#~~ these solutions reach to will be determined tomorrow.

Also the solutions under various storage conditions will be monitored for any precipitations or pH shifts over few days.

Ingredients used in the study:

Lactic Acid USP (85-1.)	Aldrich Co.
1N HCl	VWR.
Captisol	Cydex.
Aripiprazole (BMS 337039-01)	Lot # C98492(2)M

ATTACHMENT D

SIGNED M. Neeruskar DATE 5 WITNESSED AND UNDERSTOOD BY: DATE

DO NOT WRITE IN THIS MARGIN

DATE: _____ PROJ. NO. 03008 EXPT. NO. 49

SUBJECT continued . . .

All solutions on storage from batch A & B remained clear.

pH values.

Soln. A :	4.12	} No shift from original values.
soln B :	3.53	

The saturated solutions were filtered after measuring pH.

Saturated soln. of Batch A : pH = 5.2

" " " B : pH = 3.6

These samples were diluted ~~#~~ 250 times and injected on HPLC

For Details, refer to S. Borsadia's book #

~~Areas~~ Concentrations of BMS 337039-01 in these samples =

Batch A : HCl batch :

Batch B : Lactic Acid batch :

ATTACHMENT E

M. Nemkar

DATE

WITNESSED AND UNDERSTOOD BY:

Sunitas

CROSS REFERENCES:

DATE: PROJ. NO. 03008 EXPT. NO. 50

SUBJECT EFFECT OF INCREASING CONC. OF CYCLODEXTRINS (SBECD) ON EQUILIBRIUM SOLUBILITIES OF BMS-337039-01 AT VARIOUS PHS

Concentrations of cyclodextrins used in this study

SBECD (M.Wt = 2162)

5% = 0.023 M
10% = 0.045 M
15% = 0.068 M
20% = 0.09 M

HPβCD (M.Wt = 1400)

20% = 0.14 M

Procedure:

Prepare 25 ml each of 5, 10, 15 and 20% SBECD solutions and 20% HPβCD solution in water. Add excess drug to these solutions. Take initial "as is" samples. Start adjusting pH with 1N HCl.

pHs: These solutions were adjusted to the following values:

20% HPβCD	5% SBECD
4.3	6.4
4.6	5.8
4.9	5.2
	4.8
	as is

10% SBECD	15% SBECD	20% SBECD
6.4	6.4	6.4
5.8	5.8	5.8
5.2	5.2	5.2
4.8	~~5.0~~	5.0
as is	4.8	4.8
	as is	"as is"

MN

These solutions were shaken for 24 hours on a rotary shakers.

ATTACHMENT F

M. Nemukar DATE

WITNESSED AND UNDERSTOOD BY: (Sunita) DATE

DO NOT WRITE IN THIS MARGIN

DATE: _____ PROJ. NO. 03008 EXPT. NO. 50

SUBJECT: Continued...

The pHs of suspensions were recorded. The suspensions were centrifuged using ultrafiltration tubes. The filtrate was collected pH was measured and after appropriate dilution, injected on HPLC

The pH values and dilutions are as follows...

20 %HPBCD			5 % SBECD			10 % SBECD			15 % SBECD			20 % SBECD		
pH Suspension	pH filtrate	Dilution factor	pH Suspension	pH filtrate	Dilution factor	pH Suspension	pH filtrate	Dilution factor	pH Suspension	pH filtrate	Dilution factor	pH Suspension	pH filtrate	Dilution factor
4.4	4.3	100	6.4	6.4	10	6.4	6.4	10	6.4	6.4	10	6.4	6.4	10
4.6	4.6	100	5.7	5.8	100	5.7	5.8	100	5.7	5.7	100	5.7	5.8	100
4.8	4.9	100	5.1	5.2	100	5.1	5.2	100	5.1	5.2	100	5.1	5.2	100
			4.8	4.8	100	4.8	4.8	100	4.8	4.8	100	5.0	5.0	100
			As is 7.4	7.4	10	As is 7.4	7.4	10	As is 7.4	7.4	10	As is 7.4	7.4	10

HPLC Analysis was conducted by E. Borsadia. Notebook No:

Following are the solubility numbers:

pH	Solubility (mg/ml) at RT			
	5% SBECD	10% SBECD	15% SBECD	20% SBECD
7.4 as is	0.08	0.12	0.14	0.41
6.4	0.65	1.31	2.11	2.70
5.8	2.55	4.70	5.92	8.91
5.2	6.30	11.36	12.73	18.06
5.0			16.63	21.72
4.8 #1	7.29	14.51	18.19	24.96
4.8 #2	6.82	14.02	16.26	23.51

DO NOT WRITE IN THIS MARGIN

ATTACHMENT 61

SIGNED M. Newkar DATE

WITNESSED AND UNDERSTOOD BY: DATE

CASE: **MA0095 NP**

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Burton Rodney		Dec. 12, 2005
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
MANOJ NERURKAR ET AL.
APPLICATION NO: **10/642,366**
FILED: **08/14/2003**
FOR: **ARIPIPRAZOLE COMPLEX FORMULATION AND METHOD**

ART UNIT: **1623**
EXAMINER: **MAIER, LEIGH C**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF SUNITA BORSADIA

To the Commissioner for Patents and Trademarks:

SUNITA BORSADIA DECLARES AS FOLLOWS:

1. She has a Master's degree and is a scientist specializing in pharmaceutics and pharmaceutical formulations (Pharma R&D).

2. She has been employed in the above capacity at Bristol-Myers Squibb Company for 8 years.

3. She is familiar with the laboratory experiments carried out by Manoj Nerurkar concerning preparation of aripiprazole complexes with β-cyclodextrins.

4. She signed as a witness laboratory notebook entries made by Manoj Nerurkar in Notebook No. 42671, pages 122, 132, 133, 134, 135 and 136 (Attachment A, cover page, and Attachments B, C, D, E, F and G, respectively).

5. All of the above notebook pages were signed by Manoj Nerurkar prior to April 25, 2001.

6. All of the above notebook pages were witnessed by her prior to April 25, 2001.

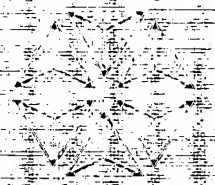
7. She is not an inventor of the subject matter claimed in U.S. Application Serial No. 10/642,366.

8. The undersigned declares further that all statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of application Serial No. 10/642,366 or any patent issued thereon.

Date: 11/28/05

Sunita Borsadia

SUNITA BORSADIA



BRISTOL-MYERS SQUIBB

PHARMACEUTICAL RESEARCH INSTITUTE

NOTEBOOK

DATE: _____ PROJ. NO. 03008 EXPT. NO. 44

SUBJEC: Timed

Solubility Screening Studies with BMS-337039 (Aripiprazole)

Solvent	Solubility, mg/mL	Data File
Water	0.0001	Nerurkam\aripi\4198
Ethanol	3.2	Nerurkam\aripi\4198026
Propylene Glycol	0.97	Nerurkam\aripi\4198018
Polyethylene Glycol 300 (PEG 300)	14.0	Nerurkam\aripi\4198019
Polyethylene Glycol 400 (PEG 400)	12.7	Nerurkam\aripi\4198020
10% Polyethylene Glycol 3350 (PEG 3350) in water	0.002	Nerurkam\aripi\4198021
Triacetin	3.5	Nerurkam\aripi\4198022
1% Egg Lecithin +1% Bile Salts (So. Cholate+deoxycholate) in water	0.05	Nerurkam\aripi\4198023
10% PVP in water	0.3	Nerurkam\aripi\4198024
N,N-Dimethyl Acetamide (DMA)	171.5	Nerurkam\aripi\4198025
10% Hydroxy propyl beta cyclodextrin in water	0.02	Nerurkam\aripi\4198027
10% Sulfabutyl ether beta cyclodextrin in water	0.12	Nerurkam\aripi\4198028
Oleic Acid	>300	-
Ethyl Oleate	1.13	Borsadis\aripi\4239005
Peanut Oil	0.86	Borsadis\aripi\4239001
Soybean Oil	0.86	Borsadis\aripi\4239002
Cottonseed Oil	1.19	Borsadis\aripi\4239003
Sesame Oil	0.82	Borsadis\aripi\4239004
Hexanoic Acid	> 200*	-
Octanoic Acid	> 200*	-
Captex (medium chain triglyceride, C8 + C10)	2.46	Borsadis\aripi\4239010
PEG 400:EtOH (50:50)	12.43	Nerurkam\aripi\4198013
PEG 400:EtOH: 1% Tween 80 in water (30:30:40)	0.35	Nerurkam\aripi\4198057
PEG 400:EtOH: 1% Solutol in water (30:30:40)	0.33	Nerurkam\aripi\4198058
Oleic Acid: Soybean Oil (10:90)	9.55 (?)	Borsadis\aripi\4239006
Oleic Acid: Soybean Oil (25:75)	29.57 (?)	Borsadis\aripi\4239007
Oleic Acid: PEG 400 (10:90)	20.23 (?)	Nerurkam\aripi\4198018
1 % Decanoic Acid in Soybean Oil	2.77	Borsadis\aripi\4239008
5 % Decanoic Acid in Soybean Oil	2.69	Borsadis\aripi\4239009

The table will be updated periodically with more studies and also when a better assay for oily systems is developed.

ATTACHMENT B

M. Nerurkar

WITNESSED AND UNDERSTOOD BY:

Gunitas

REFERENCES: Continued on Page

DATE _____ PROJ. NO. 03008 EXPT. NO. 49

SUBJECT Combination of pH adjustment & SBECD complexat

Objective of this experiment is to determine if SBECD forms a complex with Aripiprazole either in ionized or salt form of a drug.

From previous experience, we know that when the pH is adjusted with HCl, the drug gets ionized. It's solubility goes upto 0.8 mg/ml at pH 3.0. However it do not form a HCl salt (DSC on excess solid)

On the other hand, when the pH is adjusted with Lactic Acid, the solubility goes upto 8 mg/ml and the solid phase is different on DSC than the drug itself (Expt #45 pg 124). Determining solubility of drug in presence of SBECD using pH adjustment approach either with Lactic Acid or HCl will tell us if the drug forms complex, whether it is with ionized form or with lactate salt.

Batch A: pH adjustment with HCl

To about 20 ml water, add 5 g SBECD (20% SBECD in final volume of 25 ml) To this add drug (200 mg) Adjust pH with 1N HCl. Drug starts dissolving. At pH 4.0 the solution is clear.

Add 200 mg more drug – pH starts rising up. Adjust with 1N HCl. Drug completely dissolved. pH = 4.1

Add 200 mg more and adjust pH to 4.0. q.s. to 25 ml

So far 600 mg drug in 25 ml i.e about 24 mg/ml

This solution can be supersaturated or more drug may be more soluble in this medium. Filter this solution. Divide in 3 parts in 10 ml vials

Store 1 vial at RT, one at 8°C and one at -70°C

ATTACHMENT C

SIGNED M. Nemirovskaya DATE

CROSS REFERENCES:

WITNESSED AND UNDERSTOOD BY: Sunitha DATE

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DATE: PROJ. NO. 03008 EXPT. NO. 49.

SUBJECT Continued

Batch B: pH adjustment with Lactic Acid.

Perform experiment similar to this except for adjusting pH with Lactic Acid.

200 mg drug: pH 3.5 clear
+ 200 mg drug —u— u—
+ 200 mg drug —u— u—

Filter the solutions, divide and store as reported under Batch A.

To excess solutions from batch A and B, add excess drug. Equilibrate at RT. The ~~so~~ saturation solubilities at whatever pH ~~#~~ these solutions reach to will be determined tomorrow.

Also the solutions under various storage conditions will be monitored for any precipitation or pH shifts over few days.

Ingredients used in the study:

Lactic Acid USP (85%)	Aldrich Co.
1N HCl	VWR.
Captisol	Cydex.
Aripiprazole (BMS 337039-01)	Lot # C98492(2)M

ATTACHMENT D

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SIGNED M. Neeruskar DATE 5

WITNESSED AND UNDERSTOOD BY: Smith DATE

CROSS REFERENCES:

DATE: _____ PROJ. NO. 03008 EXPT. NO. 49

SUBJECT continued . . .

All solutions on storage from batch A & B remained clear.

pH values.

Soln. A : 4.12
Soln B : 3.53
} No shift from original values.

The saturated solutions were filtered after measuring pH.

Saturated soln. of Batch A : pH = 5.2
" " B : pH = 3.6

These samples were diluted ~ 250 times and injected on HPLC

For Details, refer to S. Borsadia's book #

Areas Concentrations of BMS 337039-01 in these samples =

Batch A : HCl batch :

Batch B : Lactic Acid batch :

ATTACHMENT E

M. Nemitkar DATE WITNESSED AND UNDERSTOOD BY: Sunitas

CROSS REFERENCES:

DATE: PROJ. NO. 03008 EXPT. NO. 50

SUBJECT EFFECT OF INCREASING CONC. OF CYCLODEXTRINS (SBECD) ON EQUILIBRIUM SOLUBILITIES OF BMS-337039-01 AT VARIOUS PHS

Concentrations of cyclodextrins used in this study

SBECD (M.Wt = 2162)

5% = 0.023 M
10% = 0.045 M
15% = 0.068 M
20% = 0.09 M

HPβCD (M.Wt = 1400)

20% = 0.14 M

Procedure:

Prepare 25 ml each of 5, 10, 15 and 20% SBECD solutions and 20% HPβCD solutions in water. Add excess drug to these solutions. Take initial "as is" samples. Start adjusting pH with 1N HCl.

pHs of These solutions were adjusted to the following values:

20% HPβCD	5% SBECD
4.3	6.4
4.6	5.8
4.9	5.2
	4.8
	as is

10% SBECD	15% SBECD	20% SBECD
6.4	6.4	6.4
5.8	5.8	5.8
5.2	5.2	5.2
4.8	~~5.0~~ MW	5.0
as is	4.8	4.8
	as is	"as is"

These solutions were shaken for 24 hours on a rotary shaker.

ATTACHMENT F

M. Nemukar DATE

WITNESSED AND UNDERSTOOD BY: Sunitas DATE

REFERENCES:

DO NOT WRITE IN THIS MARGIN

DATE: _____ PROJ. NO. 03008 EXPT. NO. 50

SUBJECT Continued...

The pHs of suspensions were recorded. The suspensions were centrifuged using ultrafiltration tubes. The filtrate was collected, pH was measured and after appropriate dilution, injected on HPLC

The pH values and dilutions are as follows...

20 %HPBCD			5 % SBECD			10 % SBECD			15 % SBECD			20 % SBECD		
pH Suspension	pH filtrate	Dilution factor	pH Suspension	pH filtrate	Dilution factor	pH Suspension	pH filtrate	Dilution factor	pH Suspension	pH filtrate	Dilution factor	pH Suspension	pH filtrate	Dilution factor
4.4	4.3	100	6.4	6.4	10	6.4	6.4	10	6.4	6.4	10	6.4	6.4	10
4.6	4.6	100	5.7	5.8	100	5.7	5.8	100	5.7	5.7	100	5.7	5.8	100
4.8	4.9	100	5.1	5.2	100	5.1	5.2	100	5.1	5.2	100	5.1	5.2	100
			4.8	4.8	100	4.8	4.8	100	4.8	4.8	100	5.0	5.0	100
			As is 7.4	7.4	10	As is 7.4	7.4	10	As is 7.4	7.4	10	As is 7.4	7.4	10

HPLC Analysis was conducted by S. Borsadia. Notebook No:

Following are the solubility numbers:

pH	Solubility (mg/ml) at RT			
	5% SBECD	10% SBECD	15% SBECD	20% SBECD
7.4 as is	0.08	0.12	0.14	0.41
6.4	0.65	1.31	2.11	2.70
5.8	2.55	4.70	5.92	8.91
5.2	6.30	11.36	12.73	18.06
5.0			16.63	21.72
4.8 #1	7.29	14.51	18.19	24.96
4.8 #2	6.82	14.02	16.26	23.51

ATTACHMENT 61

ED M. Nemkar DATE

S REFERENCES:

WITNESSED AND UNDERSTOOD BY: Sunitara DATE